PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2509PTWO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/14740	International filing date *(day/month/year)* 22.12.2003	Priority date *(day/month/year)* 23.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/14		
Applicant EURAND S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.07.2004	17.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Rauter, A Telephone No. +49 89 2399-8645

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14740

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-20 as originally filed

Claims, Numbers

1-20 filed with telefax on 15.02.2005

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10,15
	No:	Claims	11-14,16-20
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	11-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION V. .....

1. Reference is made to the following documents:

   D1: EP-A-1 308 156 (WO-A-2 013 792)
   D2: US-A-6 462 093
   D3: US-A-5 972 381
   D4: WO-A-9 800 113
   D5: WPI/Derwent AN-1993-408839[34] & JP-A-5 306 225

2. The present application satisfies the criteria set forth in Article 33(1) PCT with respect to claims 1 - 10, because the subject-matter of the said claims is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT), involves an inventive step (Rule 65(1)(2) PCT) and is considered industrially applicable.

   The subject-matter of claim 1 is considered new as the available prior art, *eg* D2 does not specifically disclose the teaching that in the claimed process in the irradiating step the microwave power is to be modulated as defined in step b).
   D1, similarly does not indicate the power modulation and additionally does not mention presently specified carriers. The further citations comprise teachings which are no longer relevant for the claimed subject-matter.

   The problem can be seen in the provision of further compositions having a high bioavailability of the contained drugs in amorphous form. Closest prior art represents D2, however, even if the remaining prior art is considered, the specific heat treatment step b) cannot be deduced in an obvious manner. The applicant pointed furthermore to test results which show that constant microwave power application results in completely decomposed products.

   There is no doubt that the subject-matter claimed is industrially applicable.

3. The present application does not satisfy the criterion set forth in Article 33(1) PCT with respect to claims 11 - 20, because the subject-matter of the said claims is either not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) or does not involve an inventive step (Rule 65(1)(2) PCT).

The claimed composite contains according to independent claim 11, essentially,

- cyclodextrins or maltodextrins as carrier,

and

- a drug present in amorphous form ≥ 50% with respect to the total drug present in the composite.

In claim 18, the composite is for use in therapy, and in claim 19 it is present in a composition.

Document D2 discloses in *eg* claims 7 or 8 compositions which comprise a composite comprising a drug, a cyclodextrin, and which drug is in the amorphous state (see also *eg* column 2, lines 54 - 64, *etc*). Concerning the specific embodiments of dependent claims 12 - 14, 16, 17 and 20, reference is made to claims 7, 8, 9, 10; column 3, line 19 of D2. Even if claim 15 is new, it is clearly obvious to the person skilled in the art.

There is no doubt that the subject-matter claimed is industrially applicable.

4. During the international preliminary examination procedure, the applicant has forwarded arguments concerning novelty and inventive step of present product claim 11, however they could not be considered as not reflected by the wording of the said independent claim.

AMENDED CLAIMS

1) A process for the preparation of a composite containing a drug dispersed in an organic carrier, wherein the drug is massively dispersed (in bulk) within the particles of said organic carrier and it is present in amorphous form in a quantity greater than or equal to 50%, comprising the following steps:
a) forming a mixture of a drug with an organic carrier selected from the group consisting of water-soluble complexing agents chosen from cyclodextrins and maltodextrins, water-insoluble cross-linked polymers and mixtures thereof;
b) irradiating the mixture obtained in a), with microwaves, wherein the microwave power is modulated so that the temperature of the mixture increases until it reaches a value higher than the melting temperature of the drug and it is then maintained constant at said value for at least 5 minutes.

2) Process according to claim 1, wherein in step a) a wet mixture is formed by adding a solvent.

3) Process according to claim 2, wherein said solvent is water.

4) The process according to claim 3, in which said wet mixture is formed by adding water to the carrier-drug composite in a quantity comprised of between 0.1 ml/g and 5 ml/g with respect to the dry mixture of the composite.

5) The process according to claims 2 to 4, in which the pressure at which the irradiation is carried out is comprised of between 1 and 20 bar.

6) A process according to claims 1 to 4, wherein step b) is carried out in a container constituted of a dielectric material having coupling capacity with the microwaves.

7) The process according to claim 6, wherein said dielectric material is polytetrafluoroethylene loaded with graphite.

8) The process according to the claims 1 to 7, in which the irradiation with microwaves is carried out in an power range comprised of between 100 W and 5000 W, for an overall time up to 120 minutes.

9) A process according to claims 1 to 8 wherein said cross-linked polymer is selected form the group consisting of cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, cross-linked starch, cross-linked dextran, cross-linked polystyrene and cross-linked β-cyclodextrin.

10) A process according to claims 1 to 9 wherein said drug is a drug sparingly soluble in water.

11) A composite containing a drug dispersed in carrier consisting of a water soluble complexing agent selected from cyclodextrins and maltodextrins, wherein the drug is massively dispersed (in-bulk) within the particles of said complexing agent and it is present in amorphous form in a quantity greater than or equal to 50 % by weight, with respect to the total of drug present in the composite.

12) A composite according to claim 10, wherein said cyclodextrins are selected from alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin and derivatives thereof.

13) A composite according to claims 11 or 12, wherein the drug and the carrier are present in weight ratios comprised of between 1:0.5 and 1:20.

14) A composite according to claim 13, wherein the drug and the carrier are present in weight ratios comprised of between 1:1 and 1:10.

15) A composite according to claims 11 to 14, wherein said carrier has a surface area comprised of between 0.05 m^2/g and 20 m^2/g.

16) A composite according to claims 11 to 15, wherein said drug is a drug sparingly

soluble in water.

17)A composite according to claim 16, wherein said drug is selected from nimesulide, ibuprofen, nifedipine, grisofulvine, piroxicam, progesterone, lorazepam.

18)A composite as claimed in claims 11 to 17, for use in therapy.

19)A pharmaceutical composition containing a composite as claimed in claims 11 to 18, optionally associated with pharmaceutically acceptable excipients.

20)A pharmaceutical composition according to claim 19, formulated as a granulate, pill, mini-pill, capsule, micro-capsule.